Chapter 3 - Atmospheric Chemistry and Ambient Concentrations

Pertaining to estimates of background 03 concentrations, Sections 3.4 and 3.9 were updated and expanded to more fully describe the scientific issues associated with estimating background concentrations as well as the limitations and uncertainties of the methods used to estimate them. Section 3.6 on ambient 0_3 concentrations was revised to improve the description of variability in 0_3 concentrations attributed to diurnal and seasonal patterns, and spatial differences in urban and non-urban locations.

Please comment on the adequacy of these and other changes to the chapter and recommend any revisions to improve the discussion of key information. In relation to ambient and background 0_3 concentrations, is material clearly, succinctly, and accurately provided? Where appropriate, please provide guidance that may refine the scientific interpretation and/or improve the representation of the science.

This chapter provides in general good overviews of the atmospheric chemistry relevant to ozone pollution, the ability of models to describe it, and the ozone concentration patterns over the US. The discussion of background ozone receives particular attention. We concur with the planned deletion of the supplemental section 3.9 on background ozone. Our principal concerns regarding this chapter are as follows:

- The discussion of background ozone, while overall very good, has some remediable weaknesses. Two important, newly published papers to include in the review are McDonald-Buller et al. (EST 2012) and Emery et al. (AE 2012). The McDonald-Buller paper provides a state-of-science review of strengths and weaknesses of current background ozone estimates and makes recommendations for the future. The Emery et al. paper provides a CAMx estimate of background ozone for comparison to GEOS-Chem (although it is still driven by GEOS-Chem boundary conditions). The discussion in the ISA needs to acknowledge the limitations of models in capturing the high extremes of the ozone distribution at remote sites, since these are often related to background ozone particularly in the mountainous west. The discussion of wildfire influences on ozone seems uncritical in assuming that fires are an important source of ozone, as there is substantial literature to the contrary that needs to be cited (McKeen et al. ICARTT paper, Singh et al. 2010 ARCTAS-California paper, Alvarado et al. ARCTAS Canada paper). More focus needs to be placed on background estimates relevant to the annual 4th-highest MDA8 ozone concentrations.

- The discussion of background ozone needs a better synthesis of where we stand with regard to our confidence in estimating this background, including quantitative assessment of uncertainties. The McDonald-Buller paper should be of particular value here. There should be discussion of how the information from this chapter will be used in the REA and PA and then make scientific recommendations on the inputs to those approaches.

- Long-term trends in ozone over the US warrant more attention than is presently given. These trends are important for accountability of emission controls, background influences, and effects of climate change. There is substantial literature on the topic besides EPA reports and the paper by Cooper et al. This additional literature includes the Parrish et al. paper on increasing ozone in western US inflow, the Cohan et al. paper on the accountability of SIPs, the Leibensperger et al. paper on the effect of climate change over the past three decades, the Lefohn et al.paper on trends in W126... Trends have been very non-uniform across the US, which is acknowledged in the text but would be better conveyed with maps. Discussion of differences in trends for different quantiles of the ozone distribution, and different ozone averaging times (8-h vs. 1-h) would be very useful. Trends in the frequency of exceedances of 60-70 ppb thresholds would be particularly topical. The rollback model will require a number of coefficients that are informed by the analysis of the temporal trends and how the distributions are responding to controls.

- More discussion of the western oil/gas field winter ozone scenario may be helpful in two ways. We now have 2 known areas with high winter ozone: the WY Green River Basin as noted, and the Uinta Valley (including Ouray) in UT (little to nothing is in the literature yet for this location). Understanding the relatively few and easily characterized precursor sources may add to our knowledge of many aspects of ozone formation, especially the roles of temperature and moisture. These locations may be studies of opportunity. Similar areas likely exist but are unstudied. This gap should be noted in section 3.5, monitoring networks. Another area of new concern is the massive increase in fracking activities in many parts of the country; fugitive emissions and emissions from on and off-road HDD engines are a potentially new and large source of ozone precursors.

- Some more discussion of the value of satellite observations for ozone and its precursors would be appropriate. The limited discussion of satellite observations is tepid. A more positive spin would seem to be in order given that satellite measurements have demonstrated usefulness for observing ozone in the free troposphere and for providing top-down constraints on NOx, CO, and VOC emissions.

Chapter 4 - Exposure to Ambient Ozone

Revisions made to Chapter 4 in response to CASAC comments include clarifying the discussion of the relevance of central-site monitoring data for epidemiologic studies, together with potential bias and uncertainty due to exposure error; revising the summary section to be more concise and focused on the main points of the chapter; and preparing tables to summarize field study data and facilitate comparison of exposure models. In addition, material has been added discussing averting behavior on high-0_3 concentration days.

Please comment on the adequacy of these and other changes in responding to the Panel's comments. Please provide comment on revisions that may further improve the utility of discussion for characterizing personal-ambient exposure relationships and for interpretation of epidemiologic results in subsequent chapters.

The second external review draft of Chapter 4 is a significant improvement over the first draft, not only in terms of content, but also in terms of organization and scientific accuracy. The addition of tables that summarize the results of relevant studies is welcomed, as is the addition of new information and references. The Chapter also does a good job of discussing what research is new since the last review.

Several additional changes to the Chapter are recommended. First, the Chapter should be revised to include a discussion of long-term ozone exposures, including how they relate to corresponding long-term ambient ozone concentrations and to potential confounding by co-pollutants. Since long-term personal ozone data are lacking, re-analysis of existing short-term ozone data or use of modeled exposures may be needed. Second, Section 4.5.3, which discusses results from personal exposure simulations at several NAAQS scenarios, should be reconsidered or deleted, as findings of geographic variability in the 8-h ozone exposures of children are not supported by the data. Furthermore, the section is out-of-place in the ISA and may be better suited for the Risk and Exposure Assessment. Third, as written, the analysis of population proximity to ozone monitors should be tied to maps of ozone concentrations, where ozone concentration and population data are presented together in the same analysis of monitor proximity. In absence of data, modeling results shown in Chapter 3 could be used to demonstrate whether population exposures and exposure error varies with proximity to monitors. Finally, findings from exposure studies should be integrated with discussions in Chapters 2, 6, 7, and 8, as topics related to exposure error, confounding and highly exposed populations are important considerations for these chapters.

Chapter 5 - Dosimetry and Mode of Action

Chapter 5 was reorganized and updated in response to CASAC comments, including clarification of the linkage between dosimetry and mode of action, expanded discussion of species homology and key principles of O_3 uptake, increased emphasis on underlying mechanisms which link to effects discussed in Chapters 6 and 7, and expansion of summary sections.

Please comment on the extent to which these revisions help Chapter 5 provide the underlying mechanistic and dosimetric information for interpretation of effects evidence in later chapters and recommend any revisions to improve the discussion of key information.

There have been numerous improvements in the organization and content of this chapter. The addition of an overall chapter introduction clearly lays out the goals of the chapter. The background information on respiratory tract anatomy included in this introduction is also a useful addition. The elimination of the sectional subdivisions between research in the previous ISA and newer research has improved the flow and readability of the text. Although a good effort has also been made to follow the technical suggestions made by CASAC during the previous ISA review, there is a need for further improvement in some of these areas. A brief summary of the more important improvements is given below.

As its title indicates, this chapter reviews the dosimetry of ozone including its consequent reactions in epithelial lining fluid; and discusses various MOA by which ozone and its reaction products cause health effects. Some CASAC panelists felt that that MOA might be separated from this chapter, and instead be treated in conjunction with the chapters on health effects or even as a separate chapter. As currently organized, however, the final two sections of the chapter provide a useful discussion of intersubject variability and animal homology in the context of dosimetry as well as MOA. The authors should strive

to improve the integration between the four sections within the chapter as well as their linkage to chapters 6 and 7 on short-term and long-term health effects.

Although dosimetric principles have been better explained in this second draft of the ISA, further clarification is needed. Early in the chapter, there should be a listing and definition of the various dose metrics; these definitions should be used consistently throughout the chapter. In addition, the connection between dosimetry principles and theoretical or experimental observations of dose distribution and tissue damage should be discussed in more detail.

There is also the question of whether ozone alone or toxic products of ozone reaction with endogenous substrates is responsible for adverse responses; the chapter emphasizes the importance of reaction products. This orientation relies heavily on theoretical computations suggesting that ozone reaction in the epithelial lining fluid is so fast relative to ozone diffusion that unreacted ozone cannot penetrate to epithelial cells. A description of these computations and a discussion of its underlying assumptions should be added to the chapter. To this point, some literature indicates that the liquid lining layer is so thin in some parts of the respiratory tract that ozone might indeed reach underlying tissues.

Chapters 6-7 - Integrated Health Effects of Short- and Long-Term Ozone Exposure

In Chapters 6 and 7, references to and incorporation of information from previous assessments were expanded so that the evaluation of new health evidence is more clearly integrated with the substantial existing body of evidence on ozone-related health effects. Tables, figures, and text were revised and/or created to provide additional details related to design and results of studies. In Chapter 7, the discussion of long-term exposure and mortality has been expanded with the addition of new study findings that provide additional evidence for this association.

Please comment on the extent to which there is sufficient clarity in the presentation of study designs and results. Please provide guidance where the interpretation of the scientific evidence may be improved as well as on the soundness of conclusions in these chapters.

- This chapter has been substantially improved since the last draft. Organization of the chapter is better, and figure legends have been more clearly defined. The expanded text describing the studies is an improvement.

- The text on the older studies is now more explicitly developed and integrated with the results from newer investigations and a smoother presentation of the materials is provided. Still, the focus on new scientific evidence should not be at the expense of summarizing the overall scientific evidence. The NAAQS is based on the full body of scientific evidence, not just the recent evidence. Key studies that existed during the last review should still be discussed. Although the intention to make the ISA more concise is appreciated, the document should clarify whether studies conducted since the previous review make a critical advance in the strength of evidence and their findings should be presented in the context of the previous studies. Not all previous studies need to be discussed, but key studies that still provide a basis of the overall scientific evidence should be incorporated. Tables may be useful to help summarize studies in a relatively concise manner. Rather than use a range of

potentially vague terms (e.g., "new", "recent") EPA could explicitly state that there is a focus on studies since the last review and use consistent terminology to distinguish these studies throughout.

- The studies suggesting a causal relationship for mortality are strong (see Section 6.6), and thus the assignment of a "likely" association between mortality and short-term exposure to ozone may be overly cautious. Consideration should be given to advancing to the characterization of the strength of evidence to "causal." We agree with the categories of causality for other health outcomes.

- The distinction between long-term and short-term exposure is still unclear, as Chapter 7 (long-term) has many studies that appear to be directed at acute exposure scenarios. This version of the ISA provides definition of "long-term exposure" at the start of Chapter 7, which is a useful change from the previous version; however, the inclusion of short-term studies in the long-term chapter brings that definition into question. Exposures as short as a single day are not "long-term" exposures. These studies should be moved to the short-term exposure section. Although this will split the studies on birth outcomes, the format would then be consistent with how other health outcomes are treated in the document.

- The use of standardized exposure increments is an improvement over the previous ISA as results from different studies are more easily compared. However, the words "standardized increment" should not be used in place of a numerical value. The ratio among the daily 24-hour average, daily 8-hour maximum, and daily 1-hour maximum should be consistent throughout the ISA. In the current version, multiple ratios have been applied.

- The use of evidence from outside the peer-reviewed literature is not appropriate (Adams 1998, Chapter 6).

- The claim that "there is no apparent biological mechanism to explain the association observed for short-term O_3 exposure with cardiovascular mortality (p. 6-183, line 21)" is problematic. There are several potential mechanisms, such as pulmonary inflammation.

- Additional descriptions of the human clinical studies and their implications are warranted. In particular, the ISA could provide a more clear and succinct explanation of the lowest effective exposures in human clinical studies and could describe the relationship of human clinical study protocols, including study participants, exposures, and activity patters with the "real-world" situation.

Chapter 8 - Populations Potentially at Increased Risk for Ozone-Related Health Effects

The introduction to Chapter 8 has been revised with expanded discussion to better capture the intricacies associated with characterizing populations potentially at greater risk for 03-related health effects, utilizing the terms identified by the CASAC panel (i.e. intrinsic, extrinsic, increased dose, greater exposure).

Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

Chapter 8 has been revised to incorporate language suggested by CASAC as part of the prior review in order to better define the various terms used. The chapter has moved in the right direction as a result of these revisions. Some additional revisions would help further strengthen this chapter.

1. Conceptual and definitional issues. It is important for this chapter to clearly distinguish two broad processes that can place populations at "increased risk":

1.1. Greater ambient exposure and/or greater internal dose. This includes:

> (a) persons exposed to higher levels of ambient concentrations [for example, because of where they live or because of the activities they engage in (e.g. spend more time outdoors)].
>
> (b) persons who receive a greater dose as a result of breathing pattern or who can protect themselves from high ambient concentrations resulting in a lower dose (e.g. through air conditioning).[note that this can manifest itself as effect modification in epidemiologic studies of ambient exposure, e.g. breathing pattern modifies the impact of ambient levels on disease risk, but this is not a true "synergism" it is simply due to differences in internal dose]

1.2. Greater adverse health effects given a specific dose.

> These are persons who have other characteristics that make it more likely that they will suffer adverse health effects at a given dose. These "effect modifiers" may be biological (such as genetic variations or the presence of a pre-existing disease), behavioral (e.g. nutrition) or social (such as differences in access to care that result in greater mortality when exposed to a given level of air pollution).

The term "populations-at risk" as defined in the preamble and used in chapter 8 appears to encompass both processes but this distinction could be clearer and further developed. If the terms "sensitive, vulnerable, or susceptible" populations are used anywhere in the document they need to be clearly defined. For example it needs to be clear whether "sensitive populations" (which is employed frequently throughout the document) is used as a synomym for "populations a risk" (as defined by the two processes above) or whether it refers only to populations with greater adverse health effects at a given dose.

This distinction should also be carried through in the review of the evidence (see specific comments for suggestions on how to implement this).

2. Review of the evidence. Many diverse studies are reviewed but often the evidence is not synthetically summarized. Additional synthesis highlighting the key conclusions that can be drawn from the studies would be helpful. The discussion in each section may need to reference biological mechanisms for interactions discussed elsewhere (e.g. chapter 5). It may also link to effect modification discussed in other chapters (e.g. short and long term effects chapters). It would be advantageous to develop simple

categorizations that can be used to summarize the evidence for magnification of adverse health effects by certain factors (or "effect modification"). For example strong evidence of effect modification, suggestive evidence, little or no evidence, limited data.

3. Discussion of methodologic challenges. In the conclusion section it may also be helpful to acknowledge some of the methodologic challenges inherent in studying modifiers of air pollution effects. Key among these are consistency in the measures of the effect modifiers studied and having sufficient sample size in the various cross-classified categories. These issues may explain some of the inconsistencies observed across studies. Consider integrating the section on "healthy responders" within this concluding section that highlights difficulties in investigating effect modification and notes that there is additional interindividual variability in responses which are not currently explained by known factors but need further evaluation.

Chapter 9 - Environmental Effects: Ozone Effects on Vegetation and Ecosystems

The discussion of effects in Chapter 9 has been reorganized and consolidated into fewer, but more integrated sections to lessen repetition and improve the clarity of presentation. More discussion of ecosystem modeling approaches and more consideration of ozone impacts on stomatal conductance and water cycling have been added to the chapter.

Please comment on the reorganization and content of this chapter and the adequacy, scientific soundness, and usefulness of the material presented. Please recommend any revisions to improve the discussion of key information.

The EPA has captured well and responded appropriately to the issues of concern identified by the panel after the last ISA review. It is a sound summary of the current state of knowledge of ozone effects at scales ranging from the leaf to the ecosystem. The chapter incorporates new information (since the last AQCD) on the molecular and genetic underpinnings of ozone impacts, on available comparisons of chamber-based and more recently published chamberless exposure studies, and the results of several meta-analyses that provide an integration of the previously available information. It also adequately summarizes the results of a series of ecosystem models that examine the effects of ozone on aspects of productivity.

While no major changes to the chapter are necessary, a few specific areas do need attention. These include: the reference to "sensing of ozone" by plants, which does not describe the process as currently understood; the lack of clear, unambiguous statements regarding the impact of ozone on root growth; and the lack of emphasis on ambient ozone effects on native vegetation. Further, the effect of ozone on water loss by plants (specifically, the potential for a decrease as well as potential increase in water loss due to sluggish stomata) should be incorporated into the discussion and overarching figures.

This chapter does a good job of integrating "old" and "new" research. In fact, the comparison of yield predictions based on exposure-response relationships using both open-top chamber and free air studies was compelling in its convergence, and a useful demonstration that "chamber effects" may be minimal in terms of assessing relative ozone impacts on plant growth.

As with other sections of the ISA, some technical editing is necessary (see individual comments). In addition, there's still lack of specificity and clarity about how, when and where "scale" is used. For example, the trees in the AspenFACE site are referred to as a "forest in Wisconsin" when in fact this is an artificial forest, and, at times, "ecosystem scale" is used to denote "bigger."

The addition of definitions and explanations of terms (e.g., hydraulic conductance, gross primary production, ecosystem respiration, net ecosystem production, net ecosystem exchange, photosynthesis and their relationships) would round out this chapter and make it more easily understood.

Chapter 10- The Role of Tropospheric Ozone in Climate Change and UV -B Effects

This chapter was made more concise, in part, by consolidating background material pertinent to both climate change and solar radiation into Section 1 0.1 . Section 1 0.2 was expanded and refined to clearly reflect the processes by which ozone contributes to climate change and the competing influences of ozone precursors on climate.

Please comment on the reorganization of this chapter and the adequacy, scientific soundness, and usefulness of the material presented and recommend any revisions to improve the discussion of key information.

Discussion of the importance of ozone as a climate gas is important in view of the need for concerted climate-AQ objectives in the future. Discussion of UV-B effects is also appropriate although these appear to be very small. The chapter acceptably delivers on these two topics but there are some areas of concern:

- The discussion of projections for future global emissions of ozone precursors is based on the SRES scenarios of the IPCC TAR (2001) but these have now been superseded by the IPCC AR5 RCP scenarios. While there is a need to discuss the SRES scenarios since they have been used by most of the literature until now, theISA should introduce the new RCP scenarios, which are radically different in trends of AQ gases and in particular project no increases in the future except for the business-as-usual scenario. Based on these new scenarios, it canno be assumed that tropospheric ozone will increase in the future.

- The discussion of the radiative forcing from ozone precursor emissions is inadequate. The IPCC bar chart on radiative forcing referenced to emissions would be a very important addition to this report. It would greatly help in educating the reader on the very different climate impacts of the different ozone precursors. Section 10.3.3 discusses older individual studies and gets mired into details (such as the effect of aircraft NOx) but fails to convey the consensus generated in the IPCC AR4 report on the forcings by ozone precursor emissions. The numbers in the report should be given here. In particular, an important conclusion of IPCC AR4 is that NOx emissions are climate-neutral within the range of uncertainty.

- The discussion of UV-B effects is too long relative to the importance of the effect. It rambles and needs to get more quickly to the point. Calculating UV-B effects from changes in tropospheric ozone is a relatively simple radiative transfer calculation. The effect is very small in model calculations

(Madronich et al., 2011), and undetectable in observations, as would be expected. It seems that the chapter could easily be more conclusive that the effect of expected tropospheric ozone changes on UV-B radiation is negligibly small and provide a quantitative upper limit on the effect.

Preface, Preamble, Chapters 1 (Executive Summary) and 2 (Integrative Overview)

The CASAC panel offered a number of recommendations to enhance the organization and presentation of the evidence in the ISA. An Executive Summary has been prepared and is put in the place of Chapter 1. As part of the development of the Executive Summary and restructuring of the integrative overview chapter, Chapter 1 materials have been revised and moved, specifically: (a) the more general sections on the development of the ISA and the causality framework are being placed in a Preamble that can support all ISAs; (b) the introductory sections specific to this ISA are placed at the beginning of Chapter 2; and (c) sections on legislative background and history of previous reviews are contained in a Preface in the front matter of the ISA. The intent was to bring the integrative overview discussion to the front of the document, thus making it more accessible to the reader.

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy of these summary sections and the conclusions therein.

GENERAL COMENT: The CASAC panel expresses appreciation for the major revisions that have been made in this second draft of the ISA. Particularly important are the new Preamble, Preface, Chapters 1 (Executive Summary) and 2 (Integrative Overview). For clarity we offer comments about each of these 4 sections:

Preamble

We applaud the new Preamble, which not only supports this particular ISA, but should be incorporated in other ISAs as well. Greater uniformity and clarity among CASAC documents will be helpful to the agency, to CASAC, and to the public. Further scrutiny and review of the Preamble are warranted, not because of substantial problems, but because of the potential future role of this document. We suggest that the authors of the Preamble should be identified, and that this Preamble should be submitted to an appropriate journal for peer review and publication. Alternatively, a free-standing Preamble can simply be adopted by the EPA and reviewed and endorsed by CASAC. Its substance and its future use are too important for it to be overlooked as simply part of this larger and not widely circulated document.
Of particular importance is the "framework for causal determination." Continuing clarification of this framework and using it in a consistent way will greatly improve the effectiveness and transparency of the ISAs.

The preamble would be even more effective if it included one or more flow diagrams depicting the following:

- The ISA process
- The various steps by which scientific evidence is considered and utilized, moving from ISA to REA and then to PA

- The framework for causal determination

The preamble is an ideal place to introduce key terminology and to clarify concepts. An example is to provide closure on the recent discussions between EPA and CASAC on the definition of 'vulnerable' and 'susceptible.'

The preamble needs text introducing exposure assessment and implications of the sources of the hazard identification and dose-response data with respect to the choice of whether exposure or some exposure surrogate is needed. For example, many epidemiological studies are not based on actual exposure, but use ambient concentration as a surrogate for exposure, which is subject to exposure measurement error. Exposure metrics also have implications for developing exposure management strategies. For example, on page lxiii (line 11), 'concentration-response or dose-response relationships' are mentioned, but the preamble does not adequately explain which one is used under what circumstance. It is not just the form of this function, but also the relevance of the exposure metric or surrogate to actual exposure and underlying biological processes that should be discussed.

Preamble, Page lv. We are not in agreement with the first sentence of the second paragraph, lines 15-16. Is it the case that "the most direct evidence of a causal relationship between pollutant exposures and human health effects comes from human exposure studies"? The paragraph then goes on to describe the deficiencies of such studies. An important limitation, not adequately discussed, is the necessary limitation of studies involving deliberate human exposures to outcomes that must, by definition, be trivial. More severe exacerbations, causing cardiopulmonary disease, aggravating it, or events leading to hospital admissions or mortality – all the outcomes of clinical and public health relevance – cannot be addressed in controlled human exposures. It may be true that these studies loom large at the lowest levels of observed ozone effects, but our overall concern about ozone flows more strongly from more serious outcomes detectable by epidemiology and predicted by relevant animal studies.

See also: Preamble, lxv, line 17: "….a challenge to the quantification of exposure-response relationships for ecological effects is the great regional and local variability in ecosystems." This comment suggests that spatial heterogeneity is the major issue. Equally challenging is the temporal variability in ecological systems, which is also big. Biology, whether human or not, responds nonlinearly to its environment, and it plays out temporally and spatially.

<u>Preface</u>

We very much appreciated the Preface. We agree that it makes sense to include historical aspects of ozone regulation in the preface. It's very helpful to have a time line of the ozone standard and a discussion of what has happened in the last couple of years. We like having this "story" told in one place. Is Preface the right word? Should it be called "Historic Perspective" or something like that? We applaud the complete reference list, especially all the previous ozone related documents produced by EPA. A way should be found to have all documents not protected by copyright available to the public in complete form, such as EPA publications.

The Preface explains the statutory mandate for NAAQS and review of NAAQS. The history of the NAAQS for ozone is informative. However, the last paragraph of the history omits the discrepancy between the range of levels of 0.060 to 0.070 ppm recommended by CASAC and the decision ultimately

reached by the Administrator. The text might also describe the request for CASAC to reconsider its advice, and the subsequent decision by the President to leave the current standard in place pending the current review. CASAC suggests that the most recent history of the ozone be added. It seems incomplete without Discussion of CASAC's reconsideration and the Obama decision in 2011.

Chapter 1 (Executive Summary)

We agree with the conclusion in the charge question that Chapters 1 and 2 now "comprise a useful and effective approach for presenting the summary information and conclusions." The executive summary is now seventeen pages long. That's an appropriate length. Lay people, legislators, and others can conveniently read the key points of the document. We are not concerned that several parts of this executive summary overlap with major chapters of the overall ISA. They should. The tables and figures add a lot. The summary is informative and accurate.

We have one concern. If the reader wants additional information on any particular topic, such as 1.4 Human Exposure or 1.6.4 Populations at Increased Risk, do we need to guide them to sources and expanded versions of these topics? On the one hand, the current executive summary is easy to read and uncluttered because it lacks citations. On the other hand, how does a reader of the executive summary find an expanded version of the topics addressed here? Perhaps one way is to link the major rubrics with other chapters and components of these chapters as is done in Chapter 2. Then the reader could go to those and find an expanded version of the summary as well as the references which support them.
We are concerned with the integrative and/or conceptual figures. We suggest that more attention be paid to improving them so that they become more useful. The chapter could use thorough editing. We found much of the text to be rather awkwardly written (and/or punctuated) and not always clear.
Here are some examples of points requiring clarification:

- First, ozone exposure has only been relatively consistently associated with total and cardiopulmonary mortality in the setting of short-term exposure. This is not the case for long-term exposure. The reference to consistent associations in Section 1.6.1 therefore needs to be qualified.
- Second, the lack of a discernible threshold in the concentration-response relationship is an often-repeated refrain. The evidence for this is largely based on epidemiological findings. Even though the human clinical findings, specifically on level of lung function, have demonstrated effects at lower exposure concentrations, there is evidence that effects do not occur at a concentration of 40 ppb, implying a threshold. Section 1.6.5. Ozone Concentration-Response Relationships. Here, as elsewhere in the ISA, we find the statement that there is "no indication of a threshold for O_3 concentrations greater than 30 or 40 ppb." This ignores the findings from human clinical studies showing no effects at 40 ppb.
- It seems that it is being claimed that UV-B radiation causes no health effects (Table 1-3), when these are clearly present (and documented on p. 2-48).
- A topic of importance is "policy relevant background." We don't see that addressed in the executive summary. It should be.

Chapter 2 (Integrative Overview)

This chapter on integrative health and welfare effects (Chapter 2) is a useful and concise overview.

We approve of its position in the document. There was also a consensus that greater integration – as implied in the title – would be very useful. It includes most major topics, but the pieces are not always assembled into a coherent picture. This chapter misses an opportunity for true integration: across the whole of the ISA, across disciplinary lines, across various tools (modeling, scaling models up and/or down, the integration and use of models and field studies/empirical data). It would be very useful to add "integrative" conceptual figures as well as an overarching section that is truly integrative.
Overall, this chapter was very useful and provides a broad yet somewhat detailed overview of the various topics addressed in the ISA.

Try to include more conceptual or flow diagrams, especially to illustrate integration among components of the assessment. An executive summary should convey the basic purpose, relevant context, methods, results, and conclusions. After reading Chapter 2, the reader should have a clear idea of what are the new findings compared to the prior assessment and what are the overall key findings that provide a foundation for the REA and PA.

We like the attempt at including both 2006 conclusions and current conclusions in Table 2-1 (p. 2-18). However, some 2011 concluding points are uninformative, eg, "suggestive of a causal relationship" and some are not correct (e.g,, the point on respiratory symptoms where newer findings from multi-city studies, surprisingly, weaken earlier conclusions). In current form, these tables are confusing and need attention.

Adjacent concerns for other components or for our letter to the administrator [?]:

1. Ozone concerns make clear that we need to revisit the Clean Air Act. It is now more than forty years since the Clean Air Act was passed in 1970. It has had an enormous positive influence on health and even has contributed to the economy. However, is it still possible to established air quality standards "allowing an adequate margin of safety…to protect the public health"? We are increasingly aware of susceptible individuals and it is clear that current ozone levels at the current standard have measurable health effects. Is it possible and practical to make further reductions in the standard and in ambient levels?

This problem has become more serious now that the EPA embraces a "policy relevant background" level. The ozone standard is approaching background concentrations. [Should our committee and CASAC propose that we address this problem?] While doing this, we need to be certain that we don't threaten the regulatory process and its historic successes. But if we don't address this challenge, this may also threaten the credibility of the Clean Air Act, the regulatory process and even the role of CASAC.

2. We draw attention to sections dealing with adaptation. One of the hallmarks of oxidant injury, especially ozone, is the phenomenon of adaptation. There are levels of ozone, or hyperoxia, which produce serious injury or even death in naïve animals. However, in animals chronically exposed to lower levels of ozone or oxygen, there is morphologic and biochemical adaptation. Subsequent exposures to ozone produce a far lower response. Humans exhibit the same pattern. This is important in understanding ozone toxicology in humans. It relates importantly to different patterns of ozone exposure. Citizens, who rarely see significant ozone levels and then suddenly have a two to three day episode of high ozone, may be much more affected than those who enjoy steady state ozone exposures

all the time. An adjacent topic is whether this adaptation – or attenuation – comes at a cost. Does it reflect cellular changes and remodeling that may cause harm?